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REVIEW ARTICLE

The Anticancer Efficiency of *Citrullus colocynthis* Toward the Colorectal Cancer Therapy

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Abstract

Background Colorectal cancer (CRC) remains a major cause of death worldwide. Chemotherapy is associated with some side effects during CRC treatment. Hence, proper employment of lower toxic and approaches exerting lowest side effects are essential. The *Citrullus colocynthis* (*C. colocynthis*) seems a potential anticancerous herbal medicine (HM) against CRC mostly via various efficient compounds.

Methods We performed a literature review regarding the anticancer traits of *C. colocynthis* against CRC. The possible active compounds, mechanisms, and combination therapies in vitro and in vivo or clinical trials have been also stated where found.

Results and Conclusion The anticancerous effects of *C. colocynthis* has been via a variety of pathways including apoptotic pathways (increase in caspase-3 and inhibiting STAT3 function), antioxidant and anti-inflammatory (TNF-α, nitric oxide, and pro-inflammatory cytokines such as IL-6, IL-8, and IL-1α) traits, inhibition of Wnt/β-catenin signaling pathway, and antiangiogenesis and antimetastatic effects. Future studies will be promising regarding proper application of *C. colocynthis* compounds following their extraction.

Keywords Colorectal cancer · *Citrus colocynthis* · Antioxidants · Herbal medicine · Anticancer therapy

Introduction

Colon cancer or colorectal cancer (CRC) is implicated in the malignancies of the intestinal epithelial cells which proliferate uncontrolled [1]. Most CRCs initiate with small malignant tumors and cells called adenomatous polyps, which over time can progress to the CRC. The growth and proliferation of adjacent cancer cells in the colon epithelium leads to impaired functioning of other cells ultimately leading to the dysfunction of the colon and death [2]. CRC is the third most common cancer in the world with an estimated 1,200,000 new cases per year. It is a major cause of death from cancers worldwide. The number of new cases has increased steadily since 1975 (500,000 new cases a year later). Across the world, this cancer accounts for 10% of all cancers in men and 9.4% of women [2, 3]. Epidemiology of CRC is not the same in various areas or regions of the world. While the annual incidence rate in North America and Europe reaches approximately 50 to 30 per 100,000 and is estimated to be 3–7 cases per 100,000 cases in the Middle East [2–4].

Over the past years, numerous issues have been raised about the potential variables associated with patient survival. The extent of invasion of the tumor into the intestinal epithelium, metastasis to the adjacent lymph node, and tumor metastasis to other organs are known as variables that affect the survival of patients. However, in many studies, there is a significant correlation between the stage of the cancer and its prognosis. The results of studies have revealed that the outcome of a patient with CRC depends not only on the size of the anatomical disease but also on many factors related to the patient and the tumor. It is also clear that no factor alone can determine the prognosis of the disease. On the other hand, CRC has various biologic features, therapeutic approaches, recurrence patterns, and survival rates [3–6].

CRC is graded according to its severity or involvement into four stages. In type 1, cancer has grown in the interior of the

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colon or rectum, but its release has not spread beyond the epithelium of the intestine. In grade 2, cancer has grown in the intestinal epithelium or rectum but has not reached adjacent lymph nodes. In grade 3, cancer may have affected the lymph nodes and has not yet metastasized to other body organs, while in grade 4, cancerous cells have metastasized to various parts of the body such as the lungs, kidneys, and liver [2, 3]. Epidemiological studies in recent years have revealed the highest incidence of CRC in Australia, New Zealand, North America, Canada, and parts of Europe [6–8]. Indeed, the incidence of CRC is low in Africa, Central and South Asia, China, India, and South America [2–6]. However, the incidence of this cancer is enhancing rapidly in high-income and rich countries that have recently moved from low-income economy, such as Japan, Singapore, and Eastern Europe. The main reasons for increasing the incidence of CRC in these regions mainly include dietary changes, changes in lifestyle, and factors such as smoking and obesity [7, 8].

Notably, therapeutic approaches of CRC mostly include surgery, chemotherapy, biological treatment, and radiology as well as combination therapies. However, each route has some side effects [9, 10].

Risk Factors for CRC

CRC is a multifactorial disease, in which geographic variation and different time trends in its incidence indicate environmental factors and lifestyle as major contributors to the disease. Environmental factors possibly play a crucial role in the development of CRC. The prevalence of CRC is higher in urban areas and among people with more proper socioeconomic conditions. Those major risk factors for CRC are related to nutritional behaviors or tendencies. The relationship between nutritional factors and CRC has been taken into consideration for many years, currently estimated to decrease by 30–50% by the lifestyle modification and adequate nutrition [9–11].

Noticeably, major risk factors of CRC are preventable. High fat, red meat and fried diets mainly cause direct deaths from colon and rectum cancers [8]. Additionally, diets lacking sufficient amounts of fiber, selenium, vitamins A, C, E, and D, folic acid, carotenoids, and plant phenols increase CRC risk. Obesity and physical inactivity and smoking and alcohol use are also notable. Carcinogens in tobacco cigarettes increase the incidence of CRC. Alcohol also increases the risk of CRC, even when the effect of smoking or alcohol is removed from these individuals [12]. Interestingly, aspirin and other non-steroidal anti-inflammatory drugs exhibit a preventive role in CRC. Accordingly, 30–40% reduction in the risk of adenoma and CRC may be associated with aspirin intake [8, 10].

Family History and Adenomatous Polyps

Approximately 20% of people with CRC have at least one family member with cancer history. About 85% of all CRCs constitute adenocarcinoma, which is responsible for adenomatous polyps [13]. Generally, 70 to 90% of CRC cases are adenomatous polyps. Polyps with a diameter > 2 cm have malignancy potential up to 50% [3].

Other Risk Factors

The incidence of CRC in men and women is about 40 years old reaching its peak at 50 years of age, with 92% or more diagnosed and reported. The incidence of CRC among people aged 60–79 years is more than 50 times higher than that among people younger than 40 years [14]. CRC rate is almost equal between men and women populations. The incidence and mortality rate of CRC for African Americans is higher in both genders than in white people. The risk of CRC is also related to type 2 diabetes. Women with diabetes are 1.5 times more likely to progress to CRC [8].

Symptoms, Diagnosis, and Common Therapies for CRC

Any alteration in the normal functioning of the gastrointestinal tract (GI) is considered the major symptom of CRC [12]. In general, the dominant symptoms of CRC include changes in bowel function or intestinal habits (such as diarrhea or constipation), bleeding or blood in the stool, feeling of complete intestinal emptying, abdominal pain during feces, persistent fatigue, anemia, weight loss without a clear indication, and nausea/vomiting [15].

The disease causes death in the advanced stages; hence, rapid diagnosis and treatment of the disease contribute to the patient survival. Several approaches are available to diagnose CRC; the most common of which include fecal tests to determine the existence of blood, colonoscopy, and sigmoidoscopy. Colonoscopy is considered a pivotal diagnostic method, which permits sampling of the affected area.

CRC treatment is also a variable, depending on the location of the tumor and the degree or stage of the disease. Common therapies for CRC include topical therapies, systemic therapies, surgery, laparoscopy, chemotherapy, biological therapy, and radiation therapy. Although these approaches hinder the CRC progression, most of these approaches suffer from side effects, high costs, and no desirable results. Therefore, it is pivotal to achieve an appropriate and cost-effective non-compliant treatment against the disease [16].

Apoptosis and Its Importance in Cancer

Apoptosis (programmed cell death) is a series of intracellular programmed events leading to cell death. Apoptosis results in cellular morphological deformation, cell shrinkage, nucleus shrinkage, chromatin fragmentation, and loss of adhesion that is destroyed by macrophage invasion. Apoptosis plays a crucial role in the elimination of damaged and abnormal cells. Therefore, the disorder in this process can lead to escape from death or even incomplete death of cells, which may be accompanied by destructive effects. Recent data has revealed that one of the main mechanisms for uncontrolled division and high levels of cancer cells is to escape the apoptosis process. This leads to an increase in the survival rate of cancer cells, uncontrolled division and rapid expansion, and migration and metastasis to other parts of the body. Various studies indicate that defect in apoptotic pathways can lead to accumulation of mutated cells and ultimately the onset, progression, and metastasis of the cancer, as well as death of the patient [16, 17]. Therefore, induction of apoptosis in cancer cells has been considered a promising therapeutic option, although the recognition of the factors and genes controlling this process is vital and will efficiently contribute to the treatment and control of cancer [13, 17].

Generally, apoptosis at the cell surface is regulated by the Bcl2 family proteins, pro-apoptotic protein, and antiapoptotic proteins (Bax, Bid, Bad). Along with these regulatory factors, caspases, a group of cysteine proteases, play a key role in the development of apoptosis, though being inactive in most cells [16, 18–21]. The induction of apoptosis by cell death receptors leads to the activation of initiating caspases (Caspase 8 and Caspase 9), which is associated with activation of downstream caspases and the formation of proteolytic cascades. In general, two pathways for the transmission of intracellular apoptosis have been identified. The process of apoptosis in the internal pathway is initiated by cytochrome C (Cyt-c) release from the mitochondrial membrane, which triggers caspase cascade with the contribution of other factors such as caspases 8 and 9. The release of mitochondrial proteins, in particular Cyt-c, is controlled by members of the Bcl2 protein family. The main mechanism by which Bcl2 family proteins regulate apoptosis is possibly through the Cyt-c release control. Overexpression of Bcl2 is associated with the apoptosis suppression via the inhibition of Cyt-c release. On the other hand, a group of proteins in this family such as Bid, Bad, and Bin play an important role in inducing the signal from cytosol to mitochondria and completing its role by binding to mitochondria and finalizing the action of the Bcl2 and Bcl-xL proteins [38]. For example, the Bad protein transfer from cytosol to mitochondria and binding to Bcl-xL results in the separation of Bcl-xL from Bax pro-apoptotic protein. Following the Bax release, it is oligomerized and eventually leads to the release of Cyt-c [18]. Notably, Bcl-xL binding to Bax in the absence of Bad inhibits the Bax oligomerization and Cyt-c release. On the other hand, Bid, lost by the death receptor activated caspase-8, lose the amino-terminal, as a t-bid migrating to mitochondria and inducing Bax oligomerization, eventually leading to the release of Cyt-c and apoptosis. Bad function is regulated by the process of phosphorylation and de-phosphorylation, which is performed by various cellular kinases such as MAPK. Bad phosphorylated protein is blocked by 3-3-14 cytosolic protein. This prevents the adhesion of Bad to mitochondria [20, 21].

Therefore, the association between Cyt-c, caspases and Bax and Bcl2 proteins play a key role in apoptosis induction. Increasing the expression of Bcl2, regulated by Bad proteins, inhibits the release of Cyt-c, followed by apoptosis suppression. While increasing the expression of the Bax protein, which is controlled by the regulatory function of the Bid factors, it increases the release of Cyt-c from the mitochondrial membrane, activating the caspase 9 as a signal to Cyt-c [13]. In turn, the caspase-9 process activates caspase 3, which is associated with destruction of intracellular organelles leading to cell apoptosis. On the other hand, there is a substantial correlation between the activation of caspase 8 and Bcl2, the release of Cyt-c, and eventually the activation of caspase 3 and the apoptosis. Given that Cyt-c release plays a pivotal role in apoptosis initiation and apoptosis regulation by Bcl2 and caspases, it seems that increased expression of caspase 8 leads to the activation of the Bax and then caspase 3 pathways by deactivating the Bcl2 protein playing an important role in the apoptosis induction or death of cancer cells [18, 21].

Citrullus colocynthis and Its Therapeutic Properties

Citrullus colocynthis (*C. colocynthis*) is an herbal medicine (HM) belonging to the family of pumpkins, which has a stem with ability of sleeping or climbing. This plant is commonly grown in the Mediterranean, India, Ceylon, and North Africa, as well as in Iran and in the southern provinces and desert areas, particularly in Lorestan, Fars, Kerman, Baluchistan, Lut and Yazd deserts, and Khorasan areas. It also grows well in desert areas, particularly in alkaline soils and exhibits high-level resistance to water stress and salinity. Due to its high concentration of glucoside, the fruit of this plant has a very luscious effect. Numerous studies have been accomplished toward disclosure of *C. colocynthis* medical traits, particularly among patients with diabetes, to lowering blood glucose and lipids levels and treating liver problems. In traditional medicine, the use of this plant has been proposed in cases of weak bowel movements, the intestinal paralysis and intestinal obstruction, and liver disease [22]. Colocynthine is a form of glucoside that can be crystallized as a major compound responsible for the bitter taste of this plant. Recent studies, using

gas chromatography-mass spectrometry (GC-MS) analyses on the fruit extract of this plant have revealed a variety of flavonoids and phenolic compounds. The fruit of this plant, in addition to colocynthine, contains citrulline, an oily substance (10–17% grain) and various gum and salts. Its root also contains alpha-alethrin, hentriacontane, and a few saponins. The extract of this plant includes alkaloids, flavonoids, saponins, terpenoids, and glycosides. Due to the presence of these phenolic compounds, the extract of this plant has exhibited tremendous antimicrobial, antiviral, and anticancer properties [23, 24]. In traditional medicine, Abujahl watermelon fruit is a strong laxative consumed as antiglycemia, antihypertension, antitumor, antifever, antimicrobial, and antidiabetic HM and for treatment of hemorrhoids, hyperlipidemia, gastric ulcers, urinary tract infections, rheumatism, intestinal maladaptation, and liver disease [5]. Furthermore, in some studies, the anti-inflammatory effects of this plant have been investigated in the inflammatory model developed by the carginan. Recent findings have outlined that the total extract of *C. colocynthis* contains inhibitory effects on the growth of cancerous cells [11]. Moreover, recent data has confirmed this through consumption of radioactive labeled *C. colocynthis* [6]. Some studies have revealed anti-inflammatory and antioxidant properties of aqueous extract of *C. colocynthis* [20–25]. Therefore, due to its native nature and vast therapeutic features in a variety of diseases as well as cancer cells, it has the potential as a promising anticancerous HM against CRC cells [5] mostly owing to the presence of various flavonoids and phenolic compounds in the structure of *C. colocynthis*.

It is noted that anticarcinogenic properties of the *C. colocynthis* extract are due to the presence of chemical compounds in the cucurbitacin glycosides family. Cucurbic acid is one of the compounds in the *C. colocynthis* extract playing a crucial role in inhibiting the growth and proliferation of cancer cells. For this purpose, several studies have been fulfilled on the extraction of cucurbitacin from aqueous extract of this HM separately for their antinociceptive properties.

In another study, the antinociceptive effect of the *C. colocynthis* extract was revealed to inhibit the growth of the laryngeal cancer cell line (HEP2) as well as the L-929 normal mouse fibroblast. They observed that these cytotoxic effects are dose dependent, while observing a cytotoxic dose-dependent effect in HEP2 cells. Hence, at the highest concentration (100 μg/ml), the extract completely inhibited the growth of the cells and gradually decreased the cytotoxicity effect by decreasing the dose. After 48 h of treatment with HEP2 cells at a concentration of 100 μg/ml of aqueous extract, the viability of cells was 26% compared with control L929 cells. Additionally, IC50 of HEP2 cells was 27 μg/ml. Notably, the extract of *C. colocynthis* exerts no cytotoxicity against the L929 cells [26].

Li et al. found that cucurbitacin E extracted from *C. colocynthis* inhibits the growth, proliferation, migration, and development of cancer cells by inducing phosphorylation of the eukaryotic elongation factor-2 translation and induction of apoptosis [27]. In another study, Li et al. demonstrated that cucurbitacin B extracted from *C. colocynthis* caused the death of HepG-2 cancer cells by inducing caspases and Bax2/Bcl apoptotic pathways and inhibition of the cell cycle [27].

Molecular Targets and Anticancer Mechanisms of *C. colocynthis*

Considering the vital role of free radicals in cancer progress, the consumption of antioxidant supplements that inhibit the production of free radicals and inflammation processes can incredibly improve these conditions. *C. colocynthis* extracts contain not only anticancer properties but also advantageous antioxidant and anti-inflammatory effects for preventing subsequent damage to adjacent cells. In another study, the antioxidant properties of *C. colocynthis* grown in Khuzestan, traditionally used to treat type-2 diabetes, were investigated. In this study, using the DPPH method, the maximum activity of free radical scavenging in the extract of the plant stem (IC50 12.4 μg/ml) and the minimum in leaf extract (IC50 5.46 μg/ml) was observed. Based on the results of beta-carotene and linoleic acid, the minimum antioxidant activity was reported in the fruit extract (47.08 μg/ml) and its maximum amount was in the leaves (79.78 μg/ml). In addition, the highest levels of flavonoid and phenolic compounds were observed in the stem (22.18 μg/ml) and fruit (4.09 μg/ml). They also stated that methanol extracted from different parts of the *C. colocynthis* plant had various levels of antioxidant activity [24].

Marzouk et al. investigated the effects of antiproliferation and antioxidants on human colon cancer cells (HT-29) using MTS and a modal protocol of alkalin comet. Antioxidant activity of different leaf extracts was measured by DPPH and β-carotene/linoleic acid assay. Chloroform extract from leaves conferred a high potential of inhibition of cancer cells growth. This combination significantly reduced the DNA damage caused by H2O2 (100 μM). It seems that this level of antioxidant activity is comparable with vitamin C (1 mM). Ethyl acetate, acetone, and methanol extracted from the leaves depicted the highest effect on the reduction of DPPH free radicals (IC50 113 μg/ml) [23].

Mukherjee et al. investigated the anticancer effect of the extracts of fruit juice alkaloid extracts of *C. colocynthis*. The cytotoxic effect of this extract was investigated in two stages. In the first step, the effect of *C. colocynthis* extract on the mortality rate of saltwater shrimp was investigated. In this step, the extract showed high cytotoxicity (LC50 3/30 μg/ml). In the second step, anticancer activity of this extract was studied on human cancer cells. The *C. colocynthis* extract led to significant reduction in MCF-7 and HepG-2

cells survival rate (LC50 17/230 μg/ml and LC50 12/5430 μg/ml, respectively). In our study (data not published), the aqueous extract of watermelon caused a significant decrease in the number of MCF-7 and HepG-2 cancer cells in a concentration-dependent manner which were evident even after 24 to 72 h. In another study, this extract prevented the angiogenesis of the chorioalantoic curvature of the chick embryo. It also significantly reduced the number and length of vascular splits [28].

The effect of cucurbitacin E (CuE) extracted from *C. colocynthis* was also investigated on breast cancer cells. The FCM analysis reported that CuE led to the cell cycle arrest at the G2/M phase and induced the apoptosis (possibly by inhibiting STAT3 function) [26]. Furthermore, the *C. colocynthis*–reduced inflammatory mediators such as TNF-α, nitric oxide, as well as a number of pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, and IL-1a [29]. Davoodi et al.'s results outlined a decrease in the percentage of live cancer cells treated with the extract of this fruit as compared with the control group. In addition, the expression of the caspase gene was increased significantly at 48 and 72 h after treatment with the extract. They concluded that *C. colocynthis* fruit extract could eliminate MCF-7 breast cancer cells through increased expression of caspase 3. In a study by Shukla et al., the antimetastatic and antiangiogenic potential of a natural plant cucurbitacin B (CuB) was investigated in non-small-cell lung cancer (NSCLC) cells in vivo and in vitro. CuB showed high antimetastatic and anti-invasive potentials in nanoscale concentrations. They stated that CuB inhibited metastatic NSCLC by inhibiting Wnt/β-catenin signaling pathway [30]. Adedosu et al. clarified a significant increase in essential antioxidants such as glutathione, catalase, and superoxide dismutase following *C. colocynthis* extract consumption combined with doxorubicin chemotherapy. Additionally, they observed a significant reduction in the amount of oxidative stress markers such as malondialdehyde and TNF-α [31]. Rezaei et al. demonstrated a significant antiproliferative effect by hydroalcoholic extract of *C. colocynthis* on MCF-7 and AGS cells after 24, 48, and 72 h possibly through the cell apoptosis [32].

Conclusion

CRC remains a major cause of death worldwide; hence, proper employment of lower toxic and approaches with low side effects are essential. The *C. colocynthis* seems a potential anticancerous HM against CRC mostly via various efficient compounds. The anticancerous effects of this HM has been via a variety of mechanisms including apoptotic pathways (increase in caspase-3 and inhibiting STAT3 function), antioxidant and anti-inflammatory (TNF-α, nitric oxide, and pro-inflammatory cytokines such as IL-6, IL-8, and IL-1α) traits, inhibition of Wnt/β-catenin signaling pathway, and antiangiogenesis and antimetastatic effects. Future studies will be promising regarding proper application of *C. colocynthis* compounds following their extraction.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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